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PROVISIONAL APPLICATION COVER SHEET

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This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53 (c).

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INVENTOR(s) / APPLICANT(s)

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TITLE OF THE INVENTION *(280 characters max)*

NOVEL MYCOBACTERIAL INHIBITORS

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OR
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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒	Specification	*Number of Pages*	30	☐	Application Data Sheet
☒	Claims	*Number of Claims*	9	☐	CD(s), Number ____
☒	Drawing(s)	*Number of Sheets*	0	☐	Other (specify)

METHOD OF PAYMENT *(check one)*

☐ A check or money order is enclosed to cover the Provisional filing fees. ☒ The Commissioner is hereby authorized to charge filing fees and credit any overpayment to Deposit Account No. **10-0750-PRD2183**	Provisional Filing Fee Amount ($)	$ 160.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.
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Respectfully submitted,

SIGNATURE:

REGISTRATION NO. 43,332

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DATE: January 23, 2004

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PROVISIONAL APPLICATION FILING ONLY

DOCKET NO. PRD 2183

IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

Applicant: JÉRÔME EMILE GEORGES GUILLEMONT

For : NOVEL MYCOBACTERIAL INHIBITORS

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"Express Mail" mailing number: EF 195557386US

Date of Deposit: January 23, 2004

I hereby certify that this complete Provisional application, including specification pages and claims, is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450.

A Combined Declaration and Power of Attorney will be submitted to the United States Patent and Trademark Office upon receipt of the U.S. Serial Number for this patent application.

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NOVEL MYCOBACTERIAL INHIBITORS

The present invention relates to novel substituted quinoline derivatives useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as *Mycobacterium tuberculosis, M. bovis, M. avium and M. marinum.*

BACKGROUND OF THE INVENTION

Mycobacterium tuberculosis is the causative agent of tuberculosis (TB), a serious and potentially fatal infection with a world-wide distribution. Estimates from the World Health Organization indicate that more than 8 million people contract TB each year, and 2 million people die from tuberculosis yearly. In the last decade, TB cases have grown 20% worldwide with the highest burden in the most impoverished communities. If these trends continue, TB incidence will increase by 41% in the next twenty years. Fifty years since the introduction of an effective chemotherapy, TB remains after AIDS, the leading infectious cause of adult mortality in the world. Complicating the TB epidemic is the rising tide of multi-drug- resistant strains, and the deadly symbiosis with HIV. People who are HIV-positive and infected with TB are 30 times more likely to develop active TB than people who are HIV-negative and TB is responsible for the death of one out of every three people with HIV/AIDS worldwide.

Existing approaches to treatment of tuberculosis all involve the combination of multiple agents. For example, the regimen recommended by the U.S. Public Health Service is a combination of isoniazid, rifampicin and pyrazinamide for two months, followed by isoniazid and rifampicin alone for a further four months. These drugs are continued for a further seven months in patients infected with HIV. For patients infected with multi-drug resistant strains of *M. tuberculosis*, agents such as ethambutol, streptomycin, kanamycin, amikacin, capreomycin, ethionamide, cycloserine, ciprofoxacin and ofloxacin are added to the combination therapies. There exists no single agent that is effective in the clinical treatment of tuberculosis, nor any combination of agents that offers the possibility of therapy of less than six months' duration.

There is a high medical need for new drugs that improve current treatment by enabling regimens that facilitate patient and provider compliance. Shorter regimens and those that require less supervision are the best way to achieve this. Most of the benefit from

treatment comes in the first 2 months, during the intensive, or bactericidal, phase when four drugs are given together; the bacterial burden is greatly reduced, and patients become noninfectious. The 4- to 6-month continuation, or sterilizing, phase is required to eliminate persisting bacilli and to minimize the risk of relapse. A potent sterilizing drug that shortens treatment to 2 months or less would be extremely beneficial. Drugs that facilitate compliance by requiring less intensive supervision also are needed. Obviously, a compound that reduces both the total length of treatment and the frequency of drug administration would provide the greatest benefit.

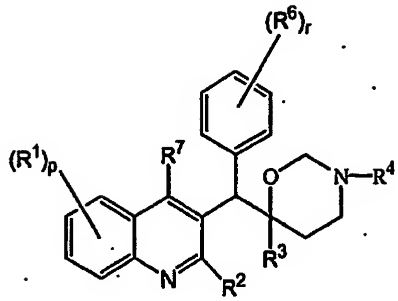
Complicating the TB epidemic is the increasing incidence of multi-drug- resistant strains or MDR-TB. Up to four percent of all cases worldwide are considered MDR-TB - those resistant to the most effective drugs of the four-drug standard, isoniazid and rifampin. MDR-TB is lethal when untreated and can not be adequately treated through the standard therapy, so treatment requires up to 2 years of "second-line" drugs. These drugs are often toxic, expensive and marginally effective. In the absence of an effective therapy, infectious MDR-TB patients continue to spread the disease, producing new infections with MDR-TB strains. There is a high medical need for a new drug with a new mechanism of action, which is likely to demonstrate activity against MDR strains.

The purpose of the present invention is to provide novel compounds, in particular substituted quinoline derivatives, having the property of inhibiting growth of mycobacteria and therefore useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as *Mycobacterium tuberculosis, M. bovis, M. avium, M. smegmatis and M. marinum.*

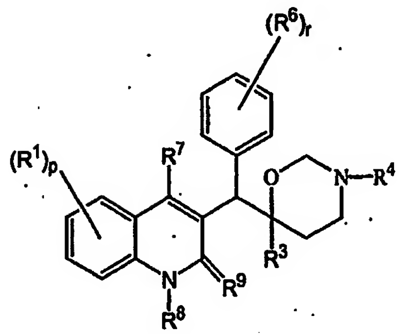
Substituted quinolines were already disclosed in US 5,965,572 (The United States of America) for treating antibiotic resistant infections and in WO 00/34265 to inhibit the growth of bacterial microorganisms. None of these publications disclose the substituted quinoline derivatives according to our invention.

SUMMARY OF THE INVENTION

The present invention relates to novel substituted quinoline derivatives according to Formula (I-A) and (I-B)



(Ia)

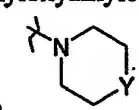


(Ib)

the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof, wherein :

R^1 is hydrogen, halo, haloalkyl, cyano, hydroxy, Ar, Het, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ;

p is an integer equal to zero, 1, 2, 3 or 4 ;

R^2 is hydrogen, hydroxy, thio, alkyloxy, alkyloxyalkyloxy, alkylthio, mono or di(alkyl)amino or a radical of formula  wherein Y is CH_2, O, S, NH or N-alkyl ;

R^3 is alkyl, Ar, Ar-alkyl, Het or Het-alkyl;

R^4 is hydrogen, alkyl or benzyl; or

R^6 is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ; or

two vicinal R^6 radicals may be taken together to form a bivalent radical of formula =C-C=C=C- ;

r is an integer equal to 0, 1, 2, 3, 4 or 5 ; and

R^7 is hydrogen, alkyl, Ar or Het ;

R^8 is hydrogen or alkyl ;

R^9 is oxo ; or

R^8 and R^9 together form the radical =N-CH=CH- .

alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo, hydroxy, alkyloxy or oxo ;

Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and mono- or dialkylaminocarbonyl ;

Het is a monocyclic heterocycle selected from the group of N-phenoxypiperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from the group of quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl ; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom with 1, 2 or 3 substituents selected from the group of halo, hydroxy, alkyl or alkyloxy ;

halo is a substituent selected from the group of fluoro, chloro, bromo and iodo and

haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, wherein one or more carbonatoms are substituted with one or more halo-atoms.

The compounds according to Formula (Ia) and (Ib) are interrelated in that e.g. a compound according to Formula (Ib), with R^9 equal to oxo is the tautomeric equivalent of a compound according to Formula (Ia) with R^2 equal to hydroxy (keto-enol tautomerism).

DETAILED DESCRIPTION

In the framework of this application, alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated

hydrocarbon radical having from 3 to 6 carbon atoms ; or is a a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo, hydroxy, alkyloxy or oxo. Preferably, alkyl is methyl, ethyl or cyclohexylmethyl.

In the framework of this application, Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and mono- or dialkylaminocarbonyl. Preferably, Ar is naphthyl or phenyl, each optionally substituted with 1 or 2 halo substituents.

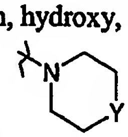
In the framework of this application, Hetis a monocyclic heterocycle selected from the group of N-phenoxypiperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from the group of quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl ; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom with 1, 2 or 3 substituents selected from the group of halo, hydroxy, alkyl or alkyloxy. Preferably, Het is thienyl.

In the framework of this application, halo is a substituent selected from the group of fluoro, chloro, bromo and iodo and haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, wherein one or more carbonatoms are substituted with one or more halo-atoms. Preferably, halo is bromo, fluoro or chloro and preferably, haloalkyl is trifluoromethyl.

Preferably, the invention relates to compounds of Formula (Ia) and (Ib) wherein :

R^1 is hydrogen, halo, cyano, Ar, Het, alkyl, and alkyloxy ;

p is an integer equal to zero, 1, 2, 3 or 4 ;

R^2 is hydrogen, hydroxy, alkyloxy, alkyloxyalkyloxy, alkylthio or a radical of formula  wherein Y is O ;

R^3 is alkyl, Ar, Ar-alkyl or Het ;
R^4 is hydrogen, alkyl or benzyl;
R^6 is hydrogen, halo or alkyl ; or
two vicinal R^6 radicals may be taken together to form a bivalent radical of formula =C-C=C=C- ;
r is an integer equal to 1 ; and
R^7 is hydrogen ;
R^8 is hydrogen or alkyl ;
R^9 is oxo ; or
R^8 and R^9 together form the radical =N-CH=CH- .
alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo or hydroxy ;
Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of halo, haloalkyl, cyano, alkyloxy and morpholinyl ;
Het is a monocyclic heterocycle selected from the group of N-phenoxypiperidinyl, furanyl, thienyl, pyridinyl, pyrimidinyl ; or a bicyclic heterocycle selected from the group of benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]-dioxolyl; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom with 1, 2 or 3 alkyl substituents ; and
halo is a substituent selected from the group of fluoro, chloro and bromo.

For compounds according to either Formula (Ia) and (Ib), preferably, R^1 is hydrogen, halo, Ar, alkyl or alkyloxy. More preferably, R^1 is halo. Most preferably, R^1 is bromo.

Preferably, p is equal to 1.

Preferably, R^2 is hydrogen, alkyloxy or alkylthio. More preferably, R^2 is alkyloxy. Most preferably, R^2 is methyloxy.

Preferably, R^3 is naphthyl, phenyl or thienyl, each optionally substituted with 1 or 2 substituents, that substituent preferably being a halo or haloalkyl, most preferably being a halo. More preferably, R^3 is naphthyl or phenyl. Most preferably, R^3 is naphthyl.

Preferably, R^4 is hydrogen or alkyl, more preferably hydrogen, methyl or ethyl, most preferably methyl.

Preferably, R^6 is hydrogen, alkyl or halo. Most preferably, R^6 is hydrogen. Preferably r is 0, 1 or 2.

Preferably, R^7 is hydrogen or methyl.

For compounds according to Formula (Ib) only, preferably, R^8 is alkyl, preferably methyl and R^9 is oxygen.

An interesting group of compounds are those compounds according to Formula (Ia), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof, in which R^1 is hydrogen, halo, Ar, alkyl or alkyloxy, p = 1, R^2 is hydrogen, alkyloxy or alkylthio, R^3 is naphthyl, phenyl or thienyl, each optionally substituted with 1 or 2 substituents selected from the group of halo and haloalkyl, R^4 is hydrogen or alkyl, R^6 is hydrogen, alkyl or halo, r is equal to 0 or 1 and R^7 is hydrogen.

The pharmaceutically acceptable acid addition salts are defined to comprise the therapeutically active non-toxic acid addition salt forms which the compounds according to either Formula (Ia) and (Ib) are able to form. Said acid addition salts can be obtained by treating the base form of the compounds according to either Formula (Ia) and (Ib) with appropriate acids, for example inorganic acids, for example hydrohalic acid, in particular hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid ; organic acids, for example acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclamic acid, salicyclic acid, p-aminosalicylic acid and pamoic acid.

The compounds according to either Formula (Ia) and (Ib) containing acidic protons may also be converted into their therapeutically active non-toxic base addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salts forms comprise, for example, the ammonium salts, the alkaline and earth alkaline metal salts, in particular lithium, sodium, potassium, magnesium and calcium salts,

salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hybramine salts, and salts with amino acids, for example arginine and lysine.

Conversely, said acid or base addition salt forms can be converted into the free forms by treatment with an appropriate base or acid.

The term addition salt as used in the framework of this application also comprises the solvates which the compounds according to either Formula (Ia) and (Ib) as well as the salts thereof, are able to form. Such solvates are, for example, hydrates and alcoholates.

The term "stereochemically isomeric forms" as used herein defines all possible isomeric forms which the compounds of either Formula (Ia) and (Ib) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration. Stereochemically isomeric forms of the compounds of either Formula (Ia) and (Ib) are obviously intended to be embraced within the scope of this invention.

Following CAS-nomenclature conventions, when two stereogenic centers of known absolute configuration are present in a molecule, an *R* or *S* descriptor is assigned (based on Cahn-Ingold-Prelog sequence rule) to the lowest-numbered chiral center, the reference center. The configuration of the second stereogenic center is indicated using relative descriptors [*R**,*R**] or [*R**,*S**], where *R** is always specified as the reference center and [*R**,*R**] indicates centers with the same chirality and [*R**,*S**] indicates centers of unlike chirality. For example, if the lowest-numbered chiral center in the molecule has an *S* configuration and the second center is *R*, the stereo descriptor would be specified as *S*-[*R**,*S**]. If "〈" and "®" are used : the position of the highest priority substituent on the asymmetric carbon atom in the ring system having the lowest ring number, is arbitrarily always in the "〈" position of the mean plane determined by the ring system. The position of the highest priority substituent on the other asymmetric carbon atom in the ring system relative to the position of the highest priority substituent on the reference atom is denominated "〈", if it is on the same side of the mean plane determined by the ring system, or "®", if it is on the other side of the mean plane determined by the ring system.

Compounds of either Formula (Ia) and (Ib) and some of the intermediate compounds invariably have at least two stereogenic centers in their structure which may lead to at least 4 stereochemically different structures.

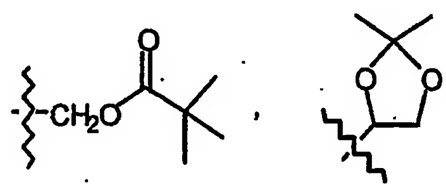
The tautomeric forms of the compounds of either Formula (Ia) and (Ib) are meant to comprise those compounds of either Formula (Ia) and (Ib) wherein e.g. an enol group is converted into a keto group (keto-enol tautomerism).

The *N*-oxide forms of the compounds according to either Formula (Ia) and (Ib) are meant to comprise those compounds of either Formula (Ia) and (Ib) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide, particularly those *N*-oxides wherein the nitrogen of the amine radical is oxidized.

The compounds of either Formula (Ia) and (Ib) as prepared in the processes described below may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of either Formula (Ia) and (Ib) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of either Formula (Ia) and (Ib) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The invention also comprises derivative compounds (usually called "pro-drugs") of the pharmacologically-active compounds according to the invention, which are degraded *in vivo* to yield the compounds according to the invention. Pro-drugs are usually (but not always) of lower potency at the target receptor than the compounds to which they are degraded. Pro-drugs are particularly useful when the desired compound has chemical or physical properties that make its administration difficult or inefficient. For example, the desired compound may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further discussion on pro-drugs may be found in Stella, V. J. *et al.*, "Prodrugs", *Drug Delivery Systems*, 1985, pp. 112-176, and *Drugs*, 1985, **29**, pp. 455-473.

Pro-drugs forms of the pharmacologically-active compounds according to the invention will generally be compounds according to either Formula (Ia) and (Ib), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof, having an acid group which is esterified or amidated. Included in such esterified acid groups are groups of the formula $-COOR^x$, where R^x is a C_{1-6}alkyl, phenyl, benzyl or one of the following groups :



Amidated groups include groups of the formula $-CONR^yR^z$, wherein R^y is H, C_{1-6}alkyl, phenyl or benzyl and R^z is –OH, H, C_{1-6}alkyl, phenyl or benzyl.

Compounds according to the invention having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This base will hydrolyze with first order kinetics in aqueous solution.

The compounds according to the invention have surprisingly been shown to be suitable for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as *Mycobacterium tuberculosis, M. bovis, M. avium, M. smegmatis and M. marinum.* The present invention thus also relates to compounds of either Formula (Ia) and (Ib) as defined hereinabove, the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof, for use as a medicine.

The invention also relates to a composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound according to the invention. The compounds according to the invention may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a

pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, in particular, for administration orally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations.

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 % by weight, more preferably from 0.1 to 70 % by weight of the active ingredient, and, from 1 to 99.95 % by weight, more preferably from 30 to 99.9 weight % of a pharmaceutically acceptable carrier, all percentages being based on the total composition.

The pharmaceutical composition may additionally contain various other ingredients known in the art, for example, a lubricant, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including

scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof. The daily dosage of the compound according to the invention will, of course, vary with the compound employed, the mode of administration, the treatment desired and the mycobacterial disease indicated. However, in general, satisfactory results will be obtained when the compound according to the invention is administered at a daily dosage not exceeding 1gram, e.g. in the range from 10 to 50 mg/kg body weight.

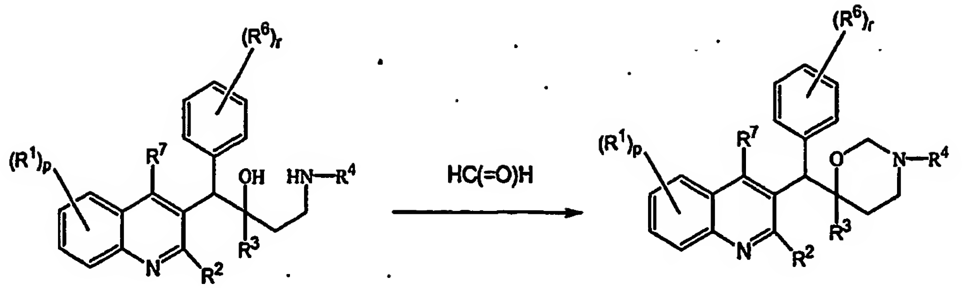
Further, the present invention also relates to the use of a compound of either Formula (Ia) and (Ib), the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof, as well as any of the aforementioned pharmaceutical compositions thereof for the manufacture of a medicament for the prevention or the treatment of mycobacterial diseases.

Accordingly, in another aspect, the invention provides a method of treating a patient suffering from , or at risk of, a mycobacterial disease, which comprises administering to the patient a therapeutically effective amount of a compound or pharmaceutical composition according to the invention.

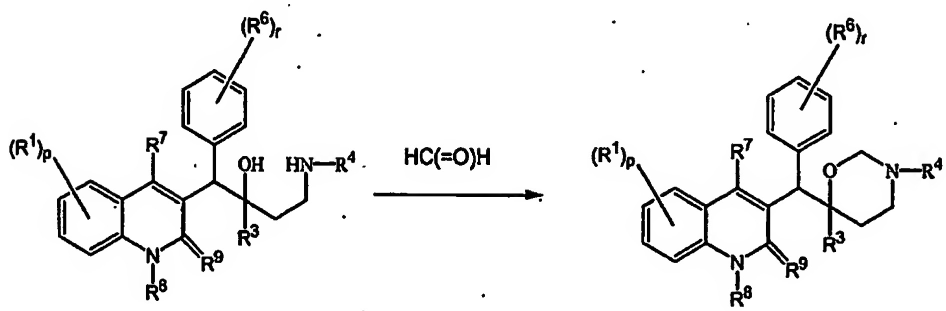
GENERAL PREPARATION

The compounds according to the invention can generally be prepared by a succession of steps, each of which is known to the skilled person.

Compounds of formula (Ia) and (Ib) can be prepared by reacting an intermediate of formula (II-a) and (II-b) with paraformaldehyde in a suitable solvent, such as for example toluene.



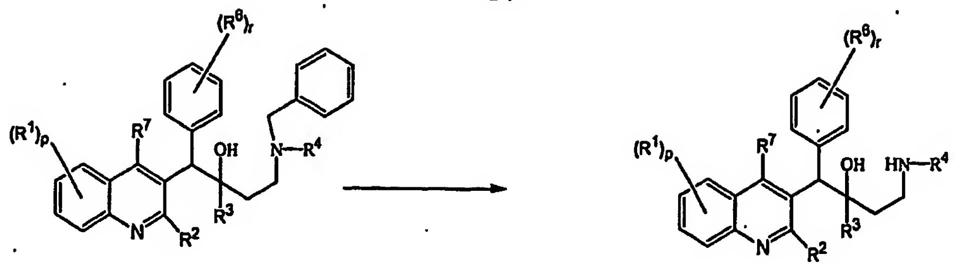
(II-a) (Ia)



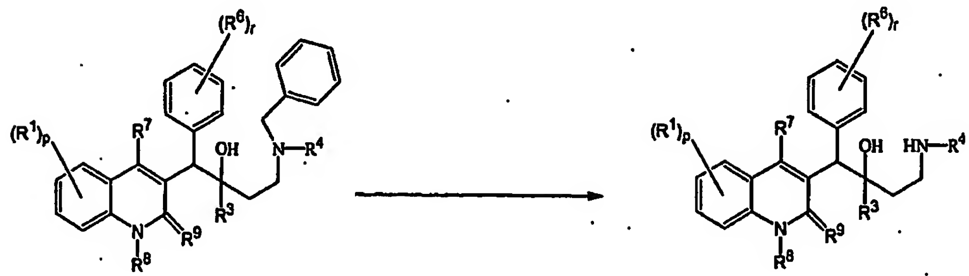
(Ib)

(II-b)

Intermediates of formula (II-a) and (II-b) can be prepared by reacting an intermediate of formula (III-a) and (III-b) with a suitable deprotecting agent, such as for example 1-chloroethyl chloroformate, in a suitable solvent, such as for example 1,2-dichloroethane and methanol.

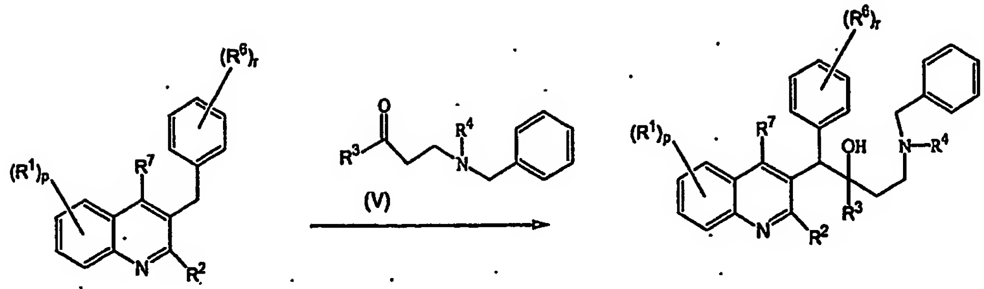


(III-a) (II-a)

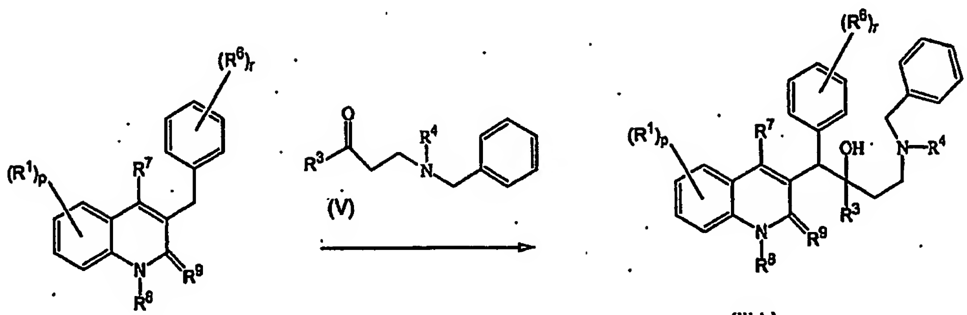


(III-b) (II-b)

Intermediates of formula (III-a) and (III-b) can be prepared by reacting an intermediate of formula (IV-a) and (IV-b) with an intermediate of formual (V) in the presence of a suitable reducing agent, such as for example n-BuLi, and in the presence of a suitable solvent, such as for example tetrahydrofuran.



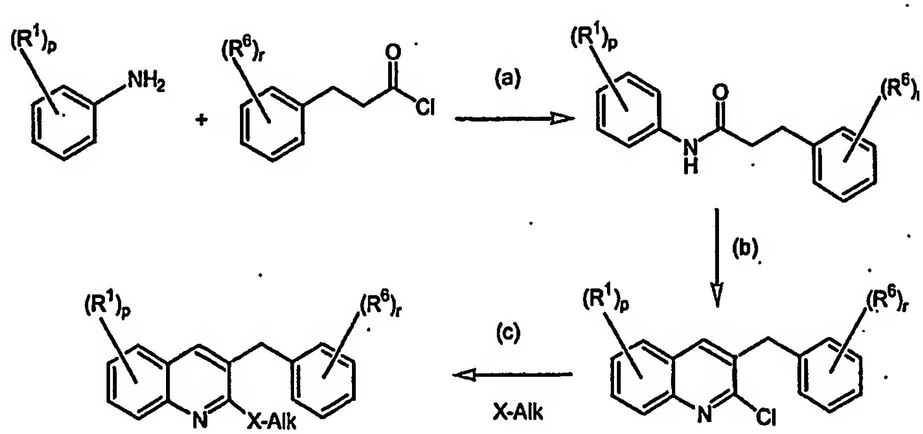
(III-a) (III-a)



(III-b) (III-b)

The intermediate compounds of (III-a) or (III-b) are compounds that are either commercially available or may be prepared according to conventional reaction procedures generally known in the art. For example, intermediates of formula (III-a-1) may be prepared according to the following reaction scheme (1):

Scheme 1



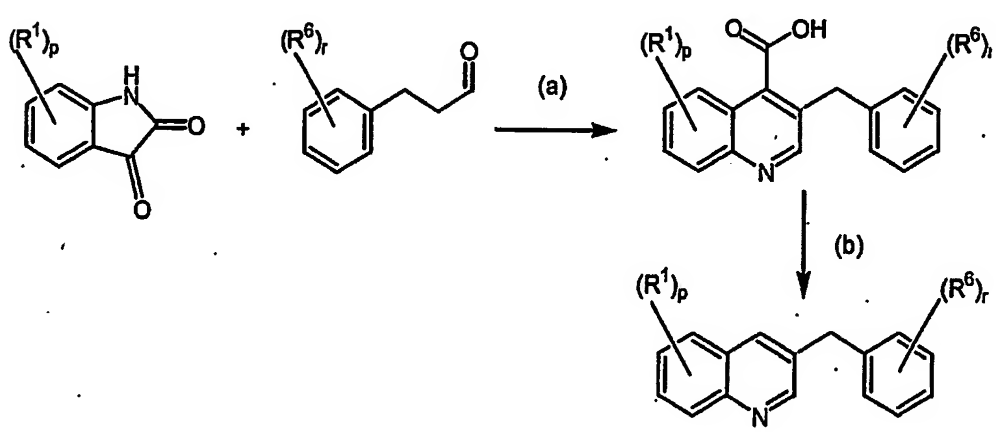
(III-a-1)

wherein all variables are defined as in Formula (Ia) and (Ib). Reaction scheme (1)

comprises step (a) in which an appropriately substituted aniline is reacted with an appropriate acylchloride such as 3-phenylpropionyl chloride, 3-fluorobenzenepropionyl chloride or p-chlorobenzenepropionyl chloride, in the presence of a suitable base, such as triethylamine and a suitable reaction-inert solvent, such as methylene chloride or ethylene dichloride. The reaction may conveniently be carried out at a temperature ranging between room temperature and reflux temperature. In a next step (b) the adduct obtained in step (a) is reacted with phosphoryl chloride ($POCl_3$) in the presence of N,N-dimethylformamide (Vilsmeier-Haack formylation followed by cyclization). The reaction may conveniently be carried out at a temperature ranging between room temperature and reflux temperature. In a next step (c) a specific R^3-group, wherein R^3 is an alkyloxy or alkylthio radical is introduced by reacting the intermediate compound obtained in step (b) with a compound X-Alk, wherein X=S or O and Alk is an alkylgroup as defined in Formula (Ia) and (Ib).

Intermediates according to Formula (III-a-2) may be prepared according to the following reaction scheme (2), wherein in a first step (a) a substituted indole-2,3-dione is reacted with a substituted 3-phenylpropionaldehyde in the presence of a suitable base such as sodium hydroxide (Pfitzinger reaction), after which the carboxylic acid compound in a next step (b) is decarboxylated at high temperature in the presence of a suitable reaction-inert solvent usch as diphenylether.

Scheme 2



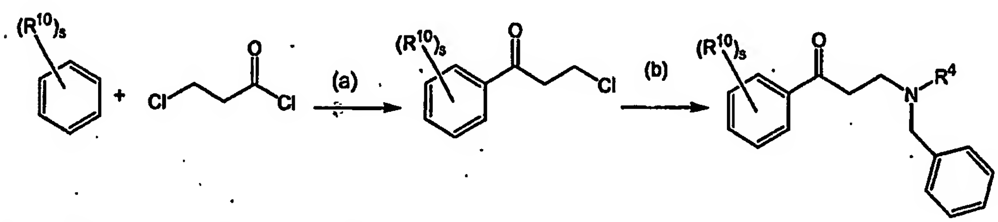
(III-a-2)

It is evident that in the foregoing and in the following reactions, the reaction products may be isolated from the reaction medium and, if necessary, further purified according

to methodologies generally known in the art, such as extraction, crystallization and chromatography. It is further evident that reaction products that exist in more than one enantiomeric form, may be isolated from their mixture by known techniques, in particular preparative chromatography, such as preparative HPLC. Typically, compounds of Formula (Ia) and (Ib) may be separated into their isomeric forms.

The intermediates of Formula (V) are compounds that are either commercially available or may be prepared according to conventional reaction procedures generally known in the art. For example, intermediate compounds of Formula (V-a) in which R^3 is Ar substituted with s substituents R^{10}, wherein each R^{10} is independently selected from the group of hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and mono- or dialkylaminocarbonyl ans s is an integer equal to zero, 1, 2 or 3, may be prepared according to the following reaction scheme (3):

Scheme 3



Reaction scheme (3) comprises step (a) in which an appropriately substituted phenyl is reacted by Friedel-Craft reaction with an appropriate acylchloride such as 3-chloropropionyl chloride or 4-chlorobutyryl chloride, in the presence of a suitable Lewis acid, such as $AlCl_3$, $FeCl_3$, $SnCl_4$, $TiCl_4$ or $ZnCl_2$ and a suitable reaction-inert solvent, such as methylene chloride or ethylene dichloride. The reaction may conveniently be carried out at a temperature ranging between room temperature and reflux temperature. In a next step (b) an amino group ($-NR_4(CH_2-C_6H_5)$) is introduced by reacting the intermediate compound obtained in step (a) with a primary or secondary amine.

The following examples illustrate the present invention without being limited thereto.

EXPERIMENTAL PART

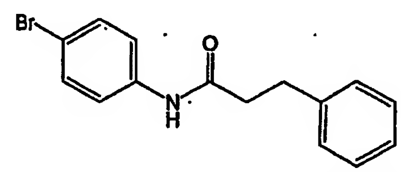
Of some compounds the absolute stereochemical configuration of the stereogenic carbon atom(s) therein was not experimentally determined. In those cases the stereochemically isomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration. However, said "A" and "B" isomeric forms can be unambiguously characterized by a person skilled in the art, using art-known methods such as, for example, X-ray diffraction. The isolation method is described in detail below.

Hereinafter, "DMF" is defined as *N,N*-dimethylformamide, "DIPE" is defined as diisopropyl ether, "THF" is defined as tetrahydrofuran.

A. Preparation of the intermediate compounds

Example A1

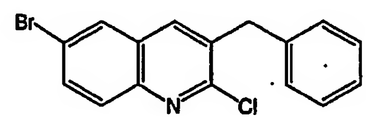
Preparation of intermediate 1



Benzenepropanoylchloride (0.488 mol) was added dropwise at room temperature to a solution of 4-bromobenzenamine (0.407 mol) in Et_3N (70ml) and CH_2Cl_2 (700ml) and the mixture was stirred at room temperature overnight. The mixture was poured out into water and concentrated NH_4OH, and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue was crystallized from diethyl ether. The residue (119.67g) was taken-up in CH_2Cl_2 and washed with HCl 1N. The organic layer was dried ($MgSO_4$), filtered, and the solvent was evaporated. Yielding: 107.67g of intermediate 1.

Example A2

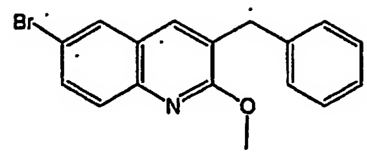
Preparation of intermediate 2



The reaction was carried out twice. $POCl_3$ (1.225 mol) was added dropwise at 10°C to DMF (0.525 mol). Then intermediate 1 (prepared according A1) (0.175 mol) was added at room temperature. The mixture was stirred overnight at 80°C, poured out on ice and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered, and the solvent was evaporated. The product was used without further purification. Yielding: 77.62g (67%) of intermediate 2.

Example A3

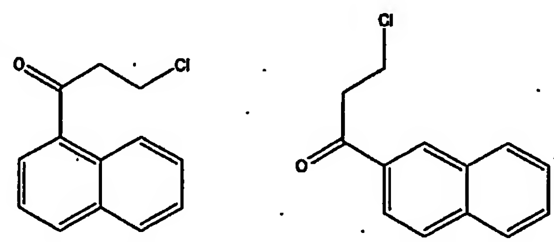
Preparation of intermediate 3



A mixture of intermediate 2 (prepared according to A2) (0.233 mol) in CH_3ONa (30%) in methanol (222.32 ml) and methanol (776ml) was stirred and refluxed overnight, then poured out on ice and extracted with CH_2Cl_2 . The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated . The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/cyclohexane 20/80 and then 100/0; 20-45μm). The pure fractions were collected and the solvent was evaporated . Yielding: 25g (33%) of intermediate 3 (mp.84°C).

Example A4

Preparation of intermediate 4 and 5

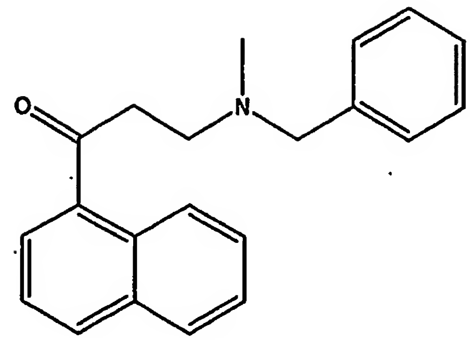


Intermediate 4 Intermediate 5

A mixture of aluminium chloride (34.3g, 0.257mol) and 3-chloropropionyl chloride (29.7g, 0.234mol) in dichloroethane (150ml) was stirred at 0°C. A solution of naphtalene (30g, 0.234mol) in dichloroethane (50ml) was added. The mixture was stirred at 5°C for 2 hours and poured out into ice water. The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (56g) was purified by column chromatography over silica gel (eluent: cyclohexane/ CH_2Cl_2: 60/40; 20-45μm). Two fractions were collected and the solvent was evaporated to afford intermediate 4 (31g, 61%) as an oil. The second fraction (14g) was taken up in DIPE to afford intermediate 5 (8.2g, 16%; mp.68°C) as a pale yellow solid.

Example A5

Preparation of intermediate 6

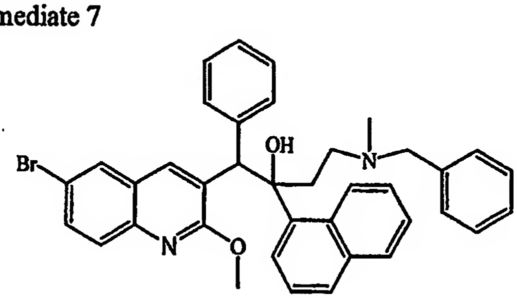


Intermediate 6

A mixture of the intermediate 4 (prepared according to A4) (3g; 0.0137mol), N-benzylmethyl amine (2ml; 0.0150mol) in acetonitrile (100ml) was stirred at 80°C for 2 hours. At room temperature (RT) water was added. The mixture was extracted with CH_2Cl_2. The organic layer was separated and dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue (6g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ MeOH: 97/3; 20-45µm) to afford an oil (4.2g; quantitative yield), yielding intermediate 6.

Example A6

Preparation of intermediate 7



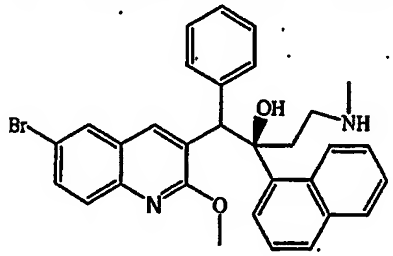
Intermediate 7

n-Butyl lithium (0.0075 mol) was added at -20°C to a solution of diisopropylamine (0.0075 mol) in THF (50ml). The mixture was cooled to -70°C. Intermediate 3 (0.0062 mol) was added. The mixture was stirred at -70°C for 1 hour and 30 minutes. Intermediate 6 (0.0075 mol) was added. The mixture was stirred for 1 hour and 30 minutes. H_2O was added. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried over magnesium sulfate, filtered, and the solvent was evaporated. The residue (3g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 90/10; 15-40µm). The pure fractions were collected and the

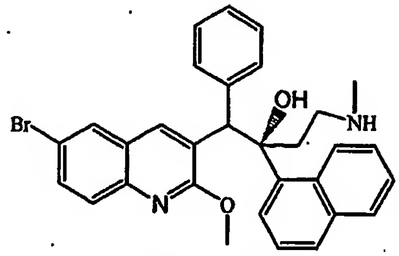
solvent was evaporated. Yielding: 1.5g of a mixture of two diastereoisomers (38%), i.e. intermediate 7.

Example A7

Preparation of intermediate 8 and 9



Intermediate 8



Intermediate 9

1-chloroethyl chloroformate (15ml) was added at room temperature to a mixture of intermediate 7 (0.0023 mol) in 1,2-dichloroethane (30ml). The mixture was stirred at 80°C for 1 hour. The solvent was evaporated. MeOH (15ml) was added. The mixture was stirred and refluxed for 30 minutes. The solvent was evaporated. The residue (1.49 g) was purified by column chromatography over silica gel (eluent : $CH_2Cl_2/MeOH/NH_4OH$ 97/3/0.1 ; 15-40µm). Two fractions were collected and the solvent was evaporated.

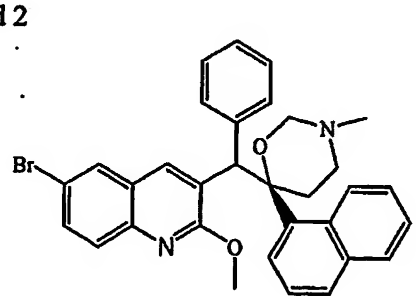
The first residue (0.23 g) was crystallized from diisopropyl ether. The precipitate was filtered off and dried. Yielding : 0.168 g (13%) of intermediate 8 (diastereoisomer A) (melting point : 204°C).

The second residue (0.32 g) was crystallized from diisopropyl ether. The precipitate was filtered off and dried. Yielding : 0.298 g (23%) of intermediate 9 (diastereoisomer B) (melting point : 225°C).

B. Preparation of the final compounds

Example B1

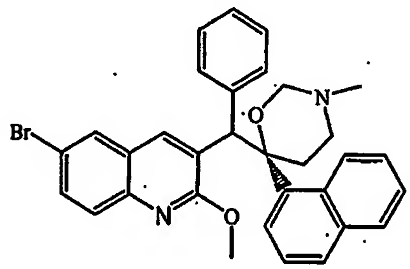
Preparation of compound 2



Compound 2

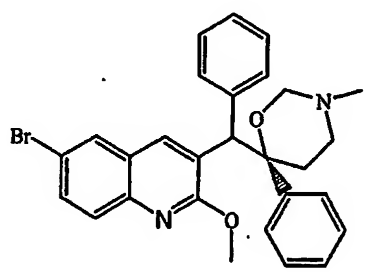
A mixture of intermediate 8 (0.00009 mol) and paraformaldehyde (0.0001 mol) in toluene (5 mL) was stirred at 80°C. The mixture was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/MeOH 99/1 ; 15-40 µm). The pure fractions were collected and the solvent was evaporated. Yieding : 0.025 g (49%) of compound 2 (diastereoisomer A) (melting point : 112°C).

Compound 1 was prepared according to the method described for compound 2. The synthesis of compound 1 yielded 0.036 g (diastereoisomer B) (71%, melting point : 108°C).



Compound 1

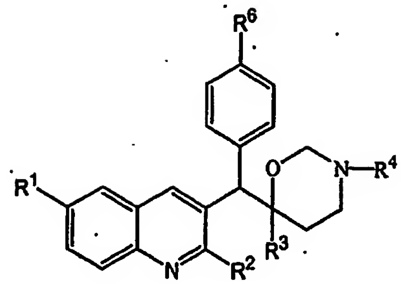
Compound 3 was also prepared according to the method described for compound 2. The phenyl analogue of intermediate 6 is a known compound. The synthesis of compound 3 yielded 0.045 g (88%) (diastereoisomer B) (melting point : 168°C).



Compound 3

The following final compounds were prepared according to the methods described above :

Table 1 :



Comp. nr.	Ex. nr.	R^1	R^2	R^3	R^6	R^4	Phys.data and stereo-chemistry
1	B1	Br	OCH_3	1-naphthyl	H	CH_3	108°C
2	B1	Br	OCH_3	1-naphthyl	H	CH_3	112°C
3	B1	Br	OCH_3	phenyl	H	CH_3	168°C

C. Pharmacological examples

C.1. In-vitro method for testing compounds against M. tuberculosis.

Flat-bottom, sterile 96-well plastic microtiter plates were filled with 100 μl of Middlebrook (1x) broth medium. Subsequently, stock solutions (10 x final test concentration) of compounds were added in 25 μl volumes to a series of duplicate wells in column 2 so as to allow evaluation of their effects on bacterial growth. Serial five-fold dilutions were made directly in the microtiter plates from column 2 to 11 using a customised robot system (Zymark Corp., Hopkinton, MA). Pipette tips were changed after every 3 dilutions to minimize pipetting errors with high hydrophobic compounds. Untreated control samples with (column 1) and without (column 12) inoculum were included in each microtiter plate. Approximately 5000 CFU per well of Mycobacterium tuberculosis (strain H37RV), in a volume of 100 μl in Middlebrook (1x) broth medium, was added to the rows A to H, except column 12. The same volume of broth medium without inoculum was added to column 12 in row A to H. The cultures were incubated at 37°C for 7 days in a humidified atmosphere (incubator with open air valve and continuous ventilation). One day before the end of incubation, 6 days after inoculation, Resazurin (1:5) was added to all wells in a volume of 20 μl and plates were incubated for another 24 hours at 37°C. On day 7 the bacterial growth was quantitated fluorometrically.

The fluorescence was read in a computer-controlled fluorometer (Spectramax Gemini EM, Molecular Devices) at an excitation wavelength of 530 nm and an emission wavelength of 590 nm. The percentage growth inhibition achieved by the compounds was calculated according to standard methods, and MIC data (representing IC90's expressed in microgram/ml) were calculated.

C.2. In-vitro method for testing compounds for anti-bacterial activity against strain M. Smegmatis ATCC607.

Flat-bottom, sterile 96-well plastic microtiter plates were filled with 180 μl of sterile deionized water, supplemented with 0.25 % BSA. Subsequently, stock solutions (7.8 x final test concentration) of compounds were added in 45 μl volumes to a series of duplicate wells in column 2 so as to allow evaluation of their effects on bacterial growth. Serial five-fold dilutions (45 μl in 180 μl) were made directly in the microtiter plates from column 2 to 11 using a customised robot system (Zymark Corp.,

Hopkinton, MA). Pipette tips were changed after every 3 dilutions to minimize pipetting errors with high hydrophobic compounds. Untreated control samples with (column 1) and without (column 12) inoculum were included in each microtiter plate. Approximately 250 CFU per well of bacteria inoculum, in a volume of 100 µl in 2.8x Mueller-Hinton broth medium, was added to the rows A to H, except column 12. The same volume of broth medium without inoculum was added to column 12 in row A to H. The cultures were incubated at 37°C for 48 hours in a humidified 5% CO_2 atmosphere (incubator with open air valve and continuous ventilation). At the end of incubation, two days after inoculation, the bacterial growth was quantitated fluorometrically. Therefore Alamar Blue (10x) was added to all wells in a volume of 20 µl and plates were incubated for another 2 hours at 50°C.

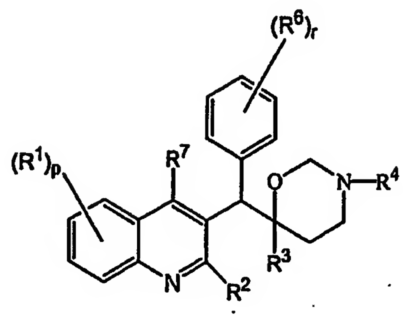
The fluorescence was read in a computer-controlled fluorometer (Cytofluor, Biosearch) at an excitation wavelength of 530 nm and an emission wavelength of 590 nm (gain 30). The % growth inhibition achieved by the compounds was calculated according to standard methods. The pIC_{50} was defined as the 50 % inhibitory concentration for bacterial growth. The results are shown in Table 2.

Table 2 : Results of an in vitro-screening of the compounds according to the invention for *M. smegmatis* (pIC_{50}).

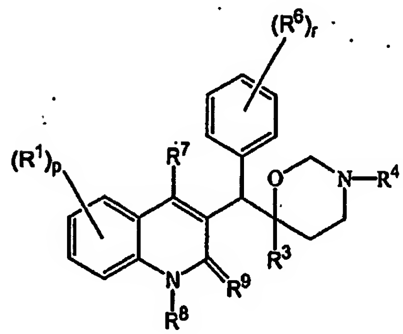
Co.No.	pIC_{50}
1	6.5
2	8.5
3	6.8

CLAIMS

1. A compound according to the general Formula (Ia) or the general Formula (Ib)



(Ia)

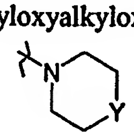


(Ib)

the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof, wherein

R^1 is hydrogen, halo, haloalkyl, cyano, hydroxy, Ar, Het, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ;

p is an integer equal to zero, 1, 2, 3 or 4 ;

R^2 is hydrogen, hydroxy, thio, alkyloxy, alkyloxyalkyloxy, alkylthio, mono or di(alkyl)amino or a radical of formula  wherein Y is CH_2, O, S, NH or N-alkyl ;

R^3 is alkyl, Ar, Ar-alkyl, Het or Het-alkyl;

R^4 is hydrogen, alkyl or benzyl; or

R^6 is hydrogen, halo, haloalkyl, hydroxy, Ar, alkyl, alkyloxy, alkylthio, alkyloxyalkyl, alkylthioalkyl, Ar-alkyl or di(Ar)alkyl ; or

two vicinal R^6 radicals may be taken together to form a bivalent radical of formula =C-C=C=C- ;

r is an integer equal to 0, 1, 2, 3, 4 or 5 ; and

R^7 is hydrogen, alkyl, Ar or Het ;

R^8 is hydrogen or alkyl ;

R^9 is oxo ; or

R^8 and R^9 together form the radical =N-CH=CH- .

alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo, hydroxy, alkyloxy or oxo ;

Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of hydroxy, halo, cyano, nitro, amino, mono- or dialkylamino, alkyl, haloalkyl, alkyloxy, haloalkyloxy, carboxyl, alkyloxycarbonyl, aminocarbonyl, morpholinyl and mono- or dialkylaminocarbonyl ;

Het is a monocyclic heterocycle selected from the group of N-phenoxypiperidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl; or a bicyclic heterocycle selected from the group of quinolinyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzofuranyl, benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl ; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom with 1, 2 or 3 substituents selected from the group of halo, hydroxy, alkyl or alkyloxy ;

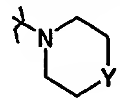
halo is a substituent selected from the group of fluoro, chloro, bromo and iodo and

haloalkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms, wherein one or more carbonatoms are substituted with one or more halo-atoms.

2. A compound according to claim 1, characterized in that

R^1 is hydrogen, halo, cyano, Ar, Het, alkyl, and alkyloxy ;

p is an integer equal to zero, 1, 2, 3 or 4 ;

R^2 is hydrogen, hydroxy, alkyloxy, alkyloxyalkyloxy, alkylthio or a radical of formula  wherein Y is O ;

R^3 is alkyl, Ar, Ar-alkyl or Het ;

R^4 is hydrogen, alkyl or benzyl;

R^6 is hydrogen, halo or alkyl ; or

two vicinal R^6 radicals may be taken together to form a bivalent radical of formula =C-C=C=C- ;

r is an integer equal to 1 ; and

R^7 is hydrogen ;

R^8 is hydrogen or alkyl ;

R^9 is oxo ; or

R^8 and R^9 together form the radical =N-CH=CH- .

alkyl is a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; or is a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms ; or is a a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms attached to a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms ; wherein each carbon atom can be optionally substituted with halo or hydroxy ;

Ar is a homocycle selected from the group of phenyl, naphthyl, acenaphthyl, tetrahydronaphthyl, each optionally substituted with 1, 2 or 3 substituents, each substituent independently selected from the group of halo, haloalkyl, cyano, alkyloxy and morpholinyl ;

Het is a monocyclic heterocycle selected from the group of N-phenoxypiperidinyl, furanyl, thienyl, pyridinyl, pyrimidinyl ; or a bicyclic heterocycle selected from the group of benzothienyl, 2,3-dihydrobenzo[1,4]dioxinyl or benzo[1,3]dioxolyl; each monocyclic and bicyclic heterocycle may optionally be substituted on a carbon atom with 1, 2 or 3 alkyl substituents ; and

halo is a substituent selected from the group of fluoro, chloro and bromo.

3. A compound according to any one of claims 1 and 2, characterized in that, independently from each other, R^1 is hydrogen, halo, Ar, alkyl or alkyloxy, p = 1, R^2 is hydrogen, alkyloxy or alkylthio, R^3 is naphthyl, phenyl or thienyl, each optionally substituted with 1 or 2 substituents selected from the group of

halo and haloalkyl, R^4 is hydrogen or alkyl, R^6 is hydrogen, alkyl or halo, r is equal to 0 or 1 and R^7 is hydrogen.

4. A compound according to claim 3, characterized in that, independently from each other, R^1 is bromo, R^2 is alkyloxy, R^3 is naphthyl or phenyl, R^4 is hydrogen, methyl or ethyl and R^6 is hydrogen.

5. A compound which is degraded in vivo to yield a compound according to any one of claims 1 to 4.

6. A compound according to any one of claims 1 to 5 for use as a medicine.

7. A composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as defined in any one of claims 1 to 5.

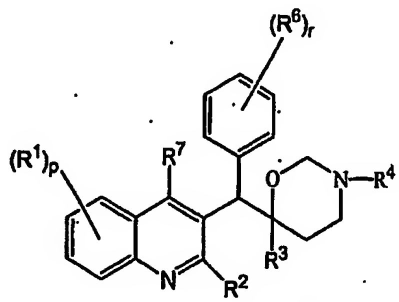
8. Use of a compound according to any one of claims 1 to 5 or a composition according to claim 7 for the manufacture of a medicament for the treatment of mycobacterial diseases.

9. Method of treating a patient suffering from, or at risk of, a mycobacterial disease, which comprises administering to the patient a therapeutically effective amount of a compound according to any one of claims 1 to 5 or pharmaceutical composition according to claim 7.

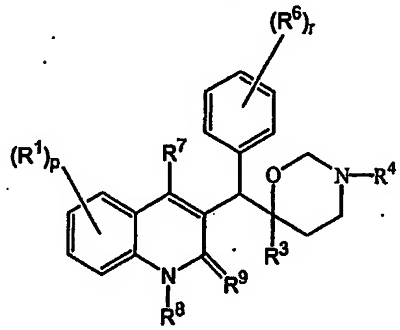
ABSTRACT

NOVEL MYCOBACTERIAL INHIBITORS

The present invention relates to novel substituted quinoline derivatives according to the general Formula (Ia) or the general Formula (Ib)



(Ia)



(Ib)

the pharmaceutically acceptable acid or base addition salts thereof, the stereochemically isomeric forms thereof, the tautomeric forms thereof and the *N*-oxide forms thereof. The claimed compounds are useful for the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as *Mycobacterium tuberculosis, M. bovis, M. avium, M. smegmatis and M. marinum.* In particular, compounds are claimed in which, independently from each other, R^1 is bromo, p=1, R^2 is alkyloxy, R^3 is optionally substituted naphthyl or phenyl, R^4 is hydrogen, methyl or ethyl, R^6 is hydrogen, r is equal to 0 or 1 and R^7 is hydrogen. Also claimed is a composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of the claimed compounds, the use of the claimed compounds or compositions for the manufacture of a medicament for the treatment of mycobacterial diseases and a process for preparing the claimed compounds.

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